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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,016	FIKSTAD ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,13-24,29-33,38,39 and 42-65* is/are pending in the application.

4a) Of the above claim(s) *44-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13-24,29-33,38,39,42 and 43* is/are rejected.

7)☒ Claim(s) *1,32-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 13-24, 29-33, 38-39 and 42-65 are presented for examination.

Applicant's Amendment and Declaration of Chandrashekar Giliyar under 37 C.F.R. 1.132 filed June 21, 2007 have each been received and entered into the present application.

Claims 1-2, 13-24, 29-33, 38-39 and 42-65 remain pending and claims 44-65 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) and MPEP §821.03. Claims 37 and 40-41 have been cancelled and claims 1-2, 17, 31-33 and 43 are amended.

Applicant's arguments, filed June 21, 2007, have been fully considered. In light of the information provided in the Interview of April 26, 2007 with Applicant's representatives David Osborne and Scott Smith, the rejection under 35 U.S.C. 102 over the Patel reference is hereby withdrawn. Additionally, rejections and objections not reiterated herein are also withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Objections to the Claims (New Grounds of Objection)

Claim 1 is objected to for misspelling the word "polyethyleneglycol" as "polethyleneglycol" in the penultimate line of the claim.

Claims 32 and 33 are also objected to for misspelling the word "polyethyleneglycol" as "polethyleneglycol" in the last line of each of the claims.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 13-24 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claim 1 is directed to a pharmaceutical composition comprising a therapeutically effective amount of a drug, a solubilizer and a release modulator that synchronizes the release of the drug and the solubilizer, such as, e.g., a "hydroxypropylmethylcellulose derivative". Present claims 32-33 are directed to, respectively, an oral dosage form or a solid oral dosage form of the same.

In particular, the specification as originally filed fails to provide adequate written support for the claim limitation directed to "a hydroxypropylmethylcellulose derivative" (claims 1, 32 and 33).

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of

DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant discloses a variety of polymeric materials for use as release modulators at page 15 of the instant specification, such as hydroxypropylmethylcellulose and cellulose derivatives. Please see p.15, l.1-18 of the present disclosure.

Applicant has failed to provide sufficient written description to support the use of "a hydroxypropylmethylcellulose derivative". In fact, the present disclosure fails to recite any structural characteristics, chemical formula, name(s) or physical characteristics such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the term "a hydroxypropylmethylcellulose derivative". Though the disclosure provided above has been noted, such teachings fail to provide a limited, let alone exemplary, teaching of what hydroxypropylmethylcellulose derivative compounds would be considered within the scope of the term "a hydroxypropylmethylcellulose derivative".

While it may be construed that the fact that the compound is based upon the parent hydroxypropylmethylcellulose compound structure implies some sort of chemical or structural characteristics sufficient to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to describe in any certain terms the degree of derivation or similarity that a compound may have from hydroxypropylmethylcellulose and still be considered a derivative for use as a release modulator of the claimed composition. The mere fact that the only chemical or structural characteristic of the compound is that it is a derivative of hydroxypropylmethylcellulose, wherein the degree of similarity or derivation from hydroxypropylmethylcellulose is herein undefined in the accompanying specification, is not sufficient to provide an adequate description of the genus of compounds intended by Applicant for use in the present invention. In the absence of such description, Applicant's limitation to "a hydroxypropylmethylcellulose

derivative" is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the genus of derivative forms of hydroxypropylmethylcellulose.

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-33 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, for the reasons of record set forth at pages 8-9 of the previous Office Action dated December 19, 2006, of which said reasons are herein incorporated by reference.

The instant rejection as it was previously set forth over claims 1-2, 13-24, 29-31 and 38-41 is **withdrawn** in view of the amendment to present claim 1.

However, Applicant has failed to amend claims 32-33 in a manner consistent with present claim 1 in order to overcome the instant rejection.

In view of such, and further in view of the fact that Applicant has failed to present any remarks or argument regarding the propriety of the present rejection as it applies to instant claims 32-33, the rejection

remains proper as it applies to such claims for the reasons of record set forth at pages 8-9 of the previous Office Action dated December 19, 2006 and is herein **maintained**.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 13-24 and 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 1 is directed to a pharmaceutical composition comprising a therapeutically effective amount of a drug, a solubilizer and a release modulator that synchronizes the release of the drug and the solubilizer, such as, e.g., a "high molecular weight polysaccharide gum". Present claims 32-33 are directed to, respectively, an oral dosage form or a solid oral dosage form of the same.

In particular, the term "high" in the phrase "high molecular weight polysaccharide gum" is a relative term that renders the claims indefinite. The term is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and, thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Use of the term "high" would invite subjective interpretations as to what molecular weight of a polysaccharide gum would be considered high and what standard against which such a weight is to be measured. As a result, one of ordinary skill in the art would not have been reasonably apprised of the metes and bounds of the claims and what would constitute infringement of the instant claims. Such subjective determinations are inconsistent with 35 U.S.C. 112, second paragraph.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 102 (New Grounds of Rejection)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 13-15, 20-24, 29, 32-33, 38 and 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Amselem et al. (U.S. Patent No. 5,891,469; 1999).

Applicant is notified that the Amselem et al. reference applies under 102(b) against the presently claimed subject matter because the instant claims are not entitled to the effective filing date of U.S. Patent Application No. 09/447,690 (November 23, 1999). Specifically, the disclosure of the '690 application fails to provide adequate written description and/or enabling direction as to the synchronized release property of the drug and the solubilizer of the composition as claimed and, therefore, fails to satisfy the conditions necessary to entitle Applicant to such a date as the effective filing date of the instant application.

Amselem teaches pharmaceutical compositions capable of increasing the oral bioavailability of a lipophilic substance (col.5, l.40-50), comprising: (1) a lipophilic substance that possesses low water solubility and poor oral bioavailability (col.1, l.21-22), such as lipophilic substances that have a water solubility of less than 50 μg/ml (col.5, l.43-47), e.g., cannabinoids (col.5, l.44), which have aqueous solubility of a few micrograms or less (i.e., meets Applicant's limitation directed to solubility of 25 μg/ml or less as stated in claim 15), (2) the surfactant alpha-tocopherol polyethylene glycol succinate (also meets Applicant's limitation directed to "tocopherol succinate", see, e.g., present claims 42-43), usually with a mean molecular weight of 1000 (col.5, l.49-66), and further (3) at least one dispersion adjuvant, such as tocopherol acetate, polyvinylpyrrolidone, a medium or long chain triglyceride and/or polyethylene glycol (col.6, l.23-26 and col.6, l.58-66). Amselem also teaches that the disclosed composition may be

administered in a therapeutically effective amount to a mammal in need of such a substance (see claim 19; col.14), wherein the substance may be in a gelatin capsule or tablet unit dosage form (see claims 9-10; col.14) and may also comprise any suitable nontoxic carrier or diluent powder or additive (col.7, l.4-15). Amselem further teaches that the lipophilic substance is present from 0.01-50% of the total solid weight of the composition, the surfactant TPGS is present from 5-65% of the total solid weight of the composition and the dispersion adjuvant is present from 5-75% of the total solid weight of the composition (col.6, l.37-57).

The teaching of tocopherol polyethyleneglycol (PEG) succinate, especially tocopherol polyethyleneglycol 1000 succinate, as the surfactant component of the disclosed pharmaceutical composition places the use of either the racemic or either enantiomeric form (d- or l-) of tocopherol PEF succinate clearly within the possession of the public. Furthermore, though Amselem et al. does not expressly recognize the "release modulating" properties of the, e.g., tocopherol PEG succinate, tocopherol acetate, polyvinylpyrrolidone, or medium or long chain triglyceride, the very teaching of the identical chemical entity in overlapping amounts clearly indicates that whatever release modulating properties that Applicant has attributed to either of these compounds are necessarily present, absent factual evidence to the contrary, since chemical compounds cannot have mutually exclusive properties. Please reference MPEP §2112.01.

With regard to present claims 20-23, directed to the solubilizer increasing the solubility of the drug by at least 25% compared to the intrinsic aqueous solubility of the drug (claim 20) or the synchronized release of the drug and solubilizer with a correlation coefficient of greater than 0.80 or 0.90 or 0.95 (claims 21-23), such correlation values are, absent factual evidence to the contrary, present in the reference because Amselem et al. teaches identical pharmaceutical formulations containing elements identical to, and capable of performing the same functions as, those elements presently claimed in the instant invention. In other words, the fact that Amselem et al. teaches identical components in what, on

its face, appears to be an identical configuration to that presently claimed, is clearly indicative of the fact that any release characteristics attributed to such a composition would be necessarily present in the prior art of Amselem et al., absent factual evidence to the contrary. Please see MPEP §2112.01[R-3] ("Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990)).

Lastly, while the limitation of "wherein the aqueous solubility of the drug is dependent on pH" in present claim 29, such is not considered to further limit the composition of parent claim 1 because such a limitation fails to impart any physical or material property to the composition that is not already present in the claim from which it depends.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 13-24, 29, 32-33, 38 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amselem et al. (U.S. Patent No. 5,891,469; 1999) in view of The Merck Index (Eleventh Edition, Monograph 3924, 1989; Pages 624-625) and Myers (U.S. Patent No. 5,891,845; 1999).

Amselem teaches pharmaceutical compositions capable of increasing the oral bioavailability of a lipophilic substance (col.5, l.40-50), comprising: (1) a lipophilic substance that possesses low water solubility and poor oral bioavailability (col.1, l.21-22), such as lipophilic substances that have a water solubility of less than 50 μg/ml (col.5, l.43-47), e.g., cannabinoids (col.5, l.44), which have aqueous solubility of a few micrograms or less (i.e., meets Applicant's limitation directed to solubility of 25 μg/ml or less as stated in claim 15), (2) the surfactant alpha-tocopherol polyethylene glycol succinate (also meets Applicant's limitation directed to "tocopherol succinate", see, e.g., present claims 42-43), usually with a mean molecular weight of 1000 (col.5, l.49-66), and further (3) at least one dispersion adjuvant, such as tocopherol acetate, polyvinylpyrrolidone, a medium or long chain triglyceride and/or polyethylene glycol (col.6, l.23-26 and col.6, l.58-66). Amselem also teaches that the disclosed composition may be administered in a therapeutically effective amount to a mammal in need of such a substance (see claim 19; col.14), wherein the substance may be in a gelatin capsule or tablet unit dosage form (see claims 9-10; col.14) and may also comprise any suitable nontoxic carrier or diluent powder or additive (col.7, l.4-15). Amselem further teaches that the lipophilic substance is present from 0.01-50% of the total solid weight of the composition, the surfactant TPGS is present from 5-65% of the total solid weight of the composition and the dispersion adjuvant is present from 5-75% of the total solid weight of the composition (col.6, l.37-57).

The teaching of tocopherol polyethyleneglycol (PEG) succinate, especially tocopherol polyethyleneglycol 1000 succinate, as the surfactant component of the disclosed pharmaceutical composition places the use of either the racemic or either enantiomeric form (d- or l-) of tocopherol PEF succinate clearly within the possession of the public. Furthermore, though Amselem et al. does not expressly recognize the "release modulating" properties of the, e.g., tocopherol PEG succinate, tocopherol acetate, polyvinylpyrrolidone, or medium or long chain triglyceride, the very teaching of the identical chemical entity in overlapping amounts clearly indicates that whatever release modulating properties that Applicant has attributed to either of these compounds are necessarily present, absent factual evidence to the contrary, since chemical compounds cannot have mutually exclusive properties. Please reference MPEP §2112.01.

With regard to present claims 20-23, directed to the solubilizer increasing the solubility of the drug by at least 25% compared to the intrinsic aqueous solubility of the drug (claim 20) or the synchronized release of the drug and solubilizer with a correlation coefficient of greater than 0.80 or 0.90 or 0.95 (claims 21-23), such correlation values are, absent factual evidence to the contrary, present in the reference because Amselem et al. teaches identical pharmaceutical formulations containing elements identical to, and capable of performing the same functions as, those elements presently claimed in the instant invention. In other words, the fact that Amselem et al. teaches identical components in what, on its face, appears to be an identical configuration to that presently claimed, is clearly indicative of the fact that any release characteristics attributed to such a composition would be necessarily present in the prior art of Amselem et al., absent factual evidence to the contrary. Please see MPEP §2112.01[R-3] ("Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are

the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990)).

Lastly, while the limitation of "wherein the aqueous solubility of the drug is dependent on pH" in present claim 29, such is not considered to further limit the composition of parent claim 1 because such a limitation fails to impart any physical or material property to the composition that is not already present in the claim from which it depends.

In view of the fact that Amselem et al. teaches the disclosed pharmaceutical compositions for formulating any of a variety of lipophilic substances, i.e., those with low water solubility and poor oral bioavailability, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use such a delivery preparation for the formulation of other highly hydrophobic drugs (i.e., those with low water solubility and, thus, poor bioavailability), such as fenofibrate, because, as The Merck Index teaches, this antihyperlipoproteinemic agent was well known in the art to be practically insoluble in water (see Monograph 3924). Accordingly, in view of the extensive hydrophobicity of both the compounds taught by Amselem et al. and fenofibrate, the skilled artisan would have had a reasonable expectation of success in effectively solubilizing fenofibrate in the delivery vehicle disclosed by Amselem et al. because of the demonstrated success in effectively solubilizing the exemplary hydrophobic agents (i.e., dexanabinol, CoQ10, etc.) of the reference into such a formulation. Further, such a person would have been motivated to do so in order to enable effective dosing of fenofibrate with concomitant enhancement of resorption and bioavailability levels, reduced variability in resorption and bioavailability levels and also a concomitant reduction in the amount required to achieve effective dosing.

Though Amselem et al. does not explicitly teach the release of the active agent over an extended period of time [i.e., more than 1 hour (claim 17), more than 2 hours (claim 18), or from 2-24 hours (claim 19)], Myers (U.S. Patent No. 5,891,845; 1999) teaches the advantages of controlled release formulations to improve the therapeutic value of the active drug component by reducing the ratio of the maximum and

minimum plasma levels (Cmax/Cmin) while maintaining such levels within the therapeutic window so as to sustain drug levels as constant effective concentrations (col.5, l.46-61) and further teaches commonly used controlled release systems, such as, e.g., dissolution and diffusion control, ion-exchange resins, osmotic devices, slow dissolving salts or complexes, or pH independent formulations (i.e., those impregnated with water insoluble waxes, such as fatty acids, carnuba wax, beeswax, or polymers, etc.; col.5, l.62-col.6, 15). In view of such teachings, one of ordinary skill in the art would have found it *prima facie* obvious to use any one or more of these well known controlled release systems in order to effect a controlled release profile of the disclosed pharmaceutical composition. Such a person would have been motivated to do in order to sustain therapeutically efficacious levels of the active agent with a concomitant reduction in the amount and frequency of dosing. The determination of the optimal range of time over which the active agent is released would have varied significantly depending on the amount to be administered, the severity of disease, the intensity of the therapeutic effect desired, toxicological and metabolic considerations, and patient compliance with a prescribed regimen. Accordingly, such a determination would have been well within the purview of, and *prima facie* obvious to, the skilled artisan and the presently claimed time ranges are not seen to be inconsistent with those that would have been determined by one of ordinary skill in the art, absent factual evidence to the contrary.

Claims 1, 13-24, 29, 32-33, 38-39 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amselem et al. (U.S. Patent No. 5,891,469; 1999) in view of The Merck Index (Eleventh Edition, Monograph 3924, 1989; Pages 624-625) and Myers (U.S. Patent No. 5,891,845; 1999), and further in view of Banker (U.S. Patent No. 3,097,144; 1963).

Amselem et al., The Merck Index and Myers et al. as applied above.

Banker teaches heat-cured polymeric film coatings for medicinal compositions that contain polyvinylpyrrolidone copolymers (title), such as, e.g., a polyvinylpyrrolidone-vinyl acetate copolymer

(col.2, l.20-27), that impart protection from moisture, reduce wear and chipping during handling and shipping and disguise unpleasant tastes (col.1, l.25-29) in solid medicinal dosage forms, such as tablets (col.1, l.23-25).

One of ordinary skill in the art would have found it *prima facie* obvious to apply the technique of coating the tablet formulation of Amselem et al. with the heat-cured polymeric film coating containing, e.g., polyvinylpyrrolidone-vinyl acetate copolymer, to improve the tablet formulation for the predictable results of imparting protection from moisture, enhancing integrity of the tablet by reducing wear and chipping that would have reasonably occurred during handling and shipping of the tablet formulations and also to enhance the aesthetics and palatability of the tablet by, for example, disguising unpleasant tastes.

Claims 1-2, 16-24, 29, 32-33 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (U.S. Patent No. 5,342,625; 1994) in view of The Merck Index (Eleventh Edition, Monograph 3924, 1989; Pages 624-625), Myers (U.S. Patent No. 5,891,845; 1999) and Lambert et al. (U.S. Patent No. 6,458,373; Issued 2002, Filed 1998).

Hauer et al. teaches pharmaceutical compositions of cyclosporine (a highly hydrophobic drug; col.3, l.22-39) that demonstrate an enhancement of resorption/bioavailability levels, as well as reduced variability in resorption/bioavailability levels in patients receiving cyclosporine therapy (col.5, l.14-31), which contain a microemulsion preconcentrate of cyclosporine, comprised of (1) a hydrophilic phase, (2) a lipophilic phase (that contains the cyclosporine) and (3) a surfactant phase, wherein the surfactant phase may contain either a single surfactant or mixture of surfactants (col.12, l.16-22), e.g., polyoxyethylene glycolated natural or hydrogenated vegetable oils (i.e., CREMOPHOR RH 40 or CREMOPHOR EL, etc.; col.9, l.48-col.10, l.13); polyoxyethylene(20) sorbitan monopalmitate, polyoxyethylene(20) sorbitan monostearate, polyoxyethylene(20) sorbitan monooleate (col.10, l.14-30); mono-, di- and mono/diglycerides (i.e., caprylic/capric acid mono- and di-glycerides; col.11, l.36-52); sorbitan

monolauryl or sorbitan monooleyl (col.11, l.53-58); glyceryl monooleate, glycerol monopalmitate, or glycerol monostearate (col.11, l.64-col.12, l.4), etc. Hauer et al. further teaches the additional inclusion of thickening agents into the composition, such as, e.g., polyacrylate and polyacrylate co-polymer resins (i.e., polyacrylic acid and polyacrylic acid/methacrylic acid resins, etc.; col.12, l.56-64); celluloses and cellulose derivatives (i.e., methyl-, ethyl-, and propyl-celluloses, hydroxypropylcellulose, etc.; col.12, l.65-col.13, l.12); polyvinylpyrrolidone copolymers (col.13, l.13-21); polyvinyl resins (i.e., gum traganth, gum arabicum, etc.; col.13, l.22-25), etc. Hauer et al. discloses the inclusion of one or more additional ingredients, including tocopherols, e.g., alpha-tocopherol (vitamin E), and teaches that the use of an anti-oxidant, in particular a tocopherol, is particularly advantageous (col.13, l.44-50). Hauer et al. teaches the following amounts of the active components for oral dosage forms (col.17, l.26-28): the cyclosporine component in an amount of 1 (or 2) to about 30% of the total weight of the composition (col.17, l.29-31), surfactant components in an amount of from about 20-90% of the total weight of the composition (col.18, l.3-12) and the thickening agents, when present, in an amount of 0.5 (or 5) up to 15 (or 20)% by weight of the total composition (col.20, l.7-13). Production of the disclosed pharmaceutical compositions may be made for filling said composition into gelatin (e.g, soft or hard) capsules (col.24, l.22-30).

Though Hauer et al. teaches the disclosed pharmaceutical compositions for formulating the highly hydrophobic drug cyclosporine, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use such a delivery preparation for the formulation of other highly hydrophobic drugs (i.e., those with low water solubility and, thus, poor bioavailability), such as fenofibrate, because, as The Merck Index teaches, this antihyperlipoproteinemic agent was well known in the art to be practically insoluble in water (see Monograph 3924). Accordingly, in view of the extensive hydrophibicity of both cyclosporine and fenofibrate, the skilled artisan would have had a reasonable expectation of success in effectively solubilizing fenofibrate in the delivery vehicle disclosed by Hauer et al. because of the demonstrated success in effectively solubilizing the hydrophobic agent cyclosporine in

such a formulation. Further, such a person would have been motivated to do so in order to enable effective dosing of fenofibrate with concomitant enhancement of resorption and bioavailability levels, reduced variability in resorption and bioavailability levels and also a concomitant reduction in the amount required to achieve effective dosing.

With regard to present claims 20-23, directed to the solubilizer increasing the solubility of the drug by at least 25% compared to the intrinsic aqueous solubility of the drug (claim 20) or the synchronized release of the drug and solubilizer with a correlation coefficient of greater than 0.80 or 0.90 or 0.95 (claims 21-23), such correlation values are, absent factual evidence to the contrary, present in the reference because Hauer et al. teaches identical pharmaceutical formulations containing elements identical to, and capable of performing the same functions as, those elements presently claimed in the instant invention. In other words, the fact that Hauer et al. teaches identical components in what, on its face, appears to be an identical configuration to that presently claimed, is clearly indicative of the fact that any release characteristics attributed to such a composition would be necessarily present in the prior art of Hauer et al., absent factual evidence to the contrary. Please see MPEP §2112.01[R-3] ("Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990)).

Lastly, while the limitation of "wherein the aqueous solubility of the drug is dependent on pH" in present claim 29, such is not considered to further limit the composition of parent claim 1 because such a limitation fails to impart any physical or material property to the composition that is not already present in the claim from which it depends.

Though Hauer et al. does not explicitly teach the release of the active agent over an extended period of time [i.e., more than 1 hour (claim 17), more than 2 hours (claim 18), or from 2-24 hours (claim 19)], Myers (U.S. Patent No. 5,891,845; 1999) teaches the advantages of controlled release formulations to improve the therapeutic value of the active drug component by reducing the ratio of the maximum and minimum plasma levels (Cmax/Cmin) while maintaining such levels within the therapeutic window so as to sustain drug levels as constant effective concentrations (col.5, l.46-61) and further teaches commonly used controlled release systems, such as, e.g., dissolution and diffusion control, ion-exchange resins, osmotic devices, slow dissolving salts or complexes, or pH independent formulations (i.e., those impregnated with water insoluble waxes, such as fatty acids, carnuba wax, beeswax, or polymers, etc.; col.5, l.62-col.6, 15). In view of such teachings, one of ordinary skill in the art would have found it *prima facie* obvious to use any one or more of these well known controlled release systems in order to effect a controlled release profile of the disclosed pharmaceutical composition. Such a person would have been motivated to do in order to sustain therapeutically efficacious levels of the active agent with a concomitant reduction in the amount and frequency of dosing. The determination of the optimal range of time over which the active agent is released would have varied significantly depending on the amount to be administered, the severity of disease, the intensity of the therapeutic effect desired, toxicological and metabolic considerations, and patient compliance with a prescribed regimen. Accordingly, such a determination would have been well within the purview of, and *prima facie* obvious to, the skilled artisan and the presently claimed time ranges are not seen to be inconsistent with those that would have been determined by one of ordinary skill in the art, absent factual evidence to the contrary.

Further, in view of the fact that Hauer et al. broadly teaches the advantage of including a tocopherol as an antioxidant of the disclosed formulation (col.13, l.44-50), one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to include various tocopherol compounds into the disclosed formulations, such as those disclosed by Lambert et al. (U.S. Patent No.

6,458,373; Issued 2002, Filed 1998), e.g., alpha-tocopherol acetate, alpha-tocopherol succinate, alpha-tocopherol nicotinate, tocopherol polyethylene glycol succinate (col.5, l.10-14, col.22, l.54-57), with the reasonable expectation of success that each of these tocopherol compounds would have retained the same or substantially similar antioxidative activity to that of alpha-tocopherol itself. Additionally, the fact that Lambert et al. teaches such alpha-tocopherol compounds as biocompatible surfactants used for the solubilization of poorly water-soluble (i.e., hydrophobic) drugs would also have motivated one of skill in the art to include any one or more of such tocopherol compounds into the formulation because such a person would have expected that the presence of such compounds would have enhanced the solubilization of the active agent, thus, resulting in a more uniform and bioavailable final product.

Claims 1-2, 16-24, 29, 32-33 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (U.S. Patent No. 5,342,625; 1994) in view of The Merck Index (Eleventh Edition, Monograph 3924, 1989; Pages 624-625), Myers (U.S. Patent No. 5,891,845; 1999), and Lambert et al. (U.S. Patent No. 6,458,373; Issued 2002, Filed 1998), and further in view of Royce (U.S. Patent No. 5,403,593; 1995).

Hauer et al., The Merck Index, Myers and Lambert et al. as applied above.

Royce teaches the use of the lipid-based glycerol ester surfactants, including, e.g., glycerol palmitostearate, glycerol distearate, etc. (col.4, l.32-50), and waxes, including, e.g., microcrystalline wax (col.4, l.67-col.5, l.2) in the formulation of therapeutically-active sustained-release type pharmaceutical preparations (abstract).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one or more of the glycerol ester type surfactants or wax components taught by Royce for use in preparing pharmaceutical preparations with a sustained, or controlled, release profile with the reasonable expectation that the use of such compound(s) would further enhance the solubilization of the hydrophobic agent. Such a person would have been clearly motivated to do so because of the

desire to enhance the bioavailability and bioabsorption of the hydrophobic therapeutic agent to be administered.

Claims 1-2, 16-24, 29, 32-33, 38-39 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (U.S. Patent No. 5,342,625; 1994) in view of The Merck Index (Eleventh Edition, Monograph 3924, 1989; Pages 624-625), Myers (U.S. Patent No. 5,891,845; 1999), and Lambert et al. (U.S. Patent No. 6,458,373; Issued 2002, Filed 1998), and further in view of Banker (U.S. Patent No. 3,097,144; 1963).

Hauer et al., The Merck Index, Myers and Lambert et al. as applied above.

Banker teaches heat-cured polymeric film coatings for medicinal compositions that contain polyvinylpyrrolidone copolymers (title), such as, e.g., a polyvinylpyrrolidone-vinyl acetate copolymer (col.2, l.20-27), that impart protection from moisture, reduce wear and chipping during handling and shipping and disguise unpleasant tastes (col.1, l.25-29) in solid medicinal dosage forms, such as tablets (col.1, l.23-25).

One of ordinary skill in the art would have found it *prima facie* obvious to apply the technique of coating the tablet formulation of Hauer et al. with the heat-cured polymeric film coating containing, e.g., polyvinylpyrrolidone-vinyl acetate copolymer, to improve the tablet formulation for the predictable results of imparting protection from moisture, enhancing integrity of the tablet by reducing wear and chipping that would have reasonably occurred during handling and shipping of the tablet formulations and also to enhance the aesthetics and palatability of the tablet by, for example, disguising unpleasant tastes.

Conclusion

Rejection of claims 1-2, 13-24, 29-33, 38-39 and 42-43 remains proper and is **maintained**.

Claims 44-65 remain **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b) and MPEP §821.03.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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August 29, 2007

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